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Cost savings from routine use of whole-genomic sequencing of six multidrug-resistant bacterial pathogens in Queensland, Australia

Louisa G. Gordon^{1,2,3}, Thomas M. Elliott¹, Brian Forde^{4,5}, Brett G. Mitchell⁶, Philip L. Russo⁷, David L. Paterson⁵, Patrick N.A. Harris^{5,8}

Affiliations:

1. QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
2. School of Nursing, Queensland University of Technology, Brisbane, Queensland, Australia.
3. School of Population Health, The University of Queensland, Brisbane, Queensland, Australia
4. School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia
5. The University of Queensland, Centre for Clinical Research, Brisbane, Queensland, Australia
6. School of Nursing and Midwifery, The University of Newcastle, Newcastle, NSW, Australia
7. School of Nursing and Midwifery, Monash University, Melbourne, Australia
8. Pathology Queensland, Queensland Health, Brisbane, Queensland, Australia

Correspondence to: Louisa Gordon, QIMR Berghofer Medical Research Institute, Population Health Department, Locked Bag 2000, Royal Brisbane Hospital, Herston, Brisbane, Australia Ph:61-7-3845 3717 Fx:61-7-3845 3502
louisa.gordon@qimrberghofer.edu.au

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Abstract

Objective: To predict the effects of routine use of whole-genome sequencing (WGS) of bacterial pathogens on healthcare costs and compare with the corresponding effects of standard of care.

Design: Budget impact analysis over the following 5 years. Data were primarily from sequencing results on clusters of multidrug-resistant organisms across 27 hospitals. Model inputs were derived from hospitalisation and sequencing data, epidemiological and costing reports, and included multidrug resistance rates and their trends.

Setting: Queensland, Australia

Participants: Hospitalised patients.

Interventions: WGS surveillance of six common multidrug-resistant organisms (*Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecium*, *Klebisella pneumoniae*, *Enterobacter specie* and *Acinetobacter baumannii*) compared with standard of care or routine microbiology testing.

Primary and secondary outcomes: Expected hospital costs, counts of patient infections and colonisations, deaths from bloodstream infections.

Results: In Year 1, 97,539 patients are expected to be infected or colonised with one of six multidrug-resistant organisms with standard of care testing. A strategy of WGS surveillance and earlier infection control measures could avoid 36,726 infected or colonised patients and avoid 650 deaths. Total costs under standard of care were AU\$170.8 million in Year 1. WGS surveillance cost an additional AU\$26.8 million but was offset by fewer costs for cleaning, nursing, personal protective equipment, shorter hospital stays and antimicrobials to produce overall cost savings of \$30.9 million in Year 1. Sensitivity analyses showed cost savings remained when input values were varied at 95% confidence limits.

Conclusions: Compared with standard of care, WGS surveillance at a statewide level could prevent substantial numbers of hospital patients infected with multidrug resistant organisms, related deaths and save healthcare costs. Primary prevention through routine use of WGS is an investment priority for the control of serious hospital-associated infections.

Key words: whole-genome sequencing, pathogen genomics, healthcare-associated infections, budget impact analysis, cost analysis

Word count (main text): 2766

Article Summary

Strengths and Limitations of this study

- This is the first study to assess the projected budget impact for a local government to invest in routine whole-genome sequencing of serious bacterial pathogens to assist hospital infection control teams.
- Analyses relied on recent outcomes from sequencing data to identify clusters, hospitalisation data, prevalence of healthcare-associated infections, and detailed costing of all hospital resources while sensitivity analyses assessed variation in inputs and the stability of the results.
- Projected cost savings of a whole genome sequencing strategy relies on the success of infection control teams to act decisively and effectively on the information of patient clusters.

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Introduction

Healthcare-associated infections (HAIs) are the most common complications in hospitalised patients in Australia¹. The associated economic burden is enormous resulting in longer hospital stays, higher treatment costs and in severe cases, intensive care unit stays and bed closures. Rates of bacterial infections causing septicaemia and deaths rose from the 1980s but has stabilised since 2000². Consequently, substantial resources are devoted to controlling HAIs, especially for multidrug resistant organisms (MROs), with strict infection control practices operating in most hospitals.

Whole-genome sequencing (WGS) of pathogens can identify genetically related isolates and identify patients involved in an outbreak. WGS can confirm or refute suspected related cases of infectious pathogens, discriminate between different strains, and classify novel pathogens³. By detecting different strains with varied transmissibility, patients can be better managed by the infection control team. Currently, usual laboratory tests to confirm infectious pathogens do not provide this granular information on different strains. Through WGS, multiple isolates can be analysed together to uncover the evolution of the pathogen (phylogenetics) and transmission history (who infected whom). In the future, sequencing is expected to identify information about resistance to certain antibiotics which has potential to guide antibiotic treatment.

There is an emerging body of work on the economic value of WGS surveillance in hospital practice⁴⁻⁶. While WGS of human tissue can be expensive⁷, bacterial and viral genomes are less complex and the sequencing cost is less than one-tenth that for a human genome⁵. Nevertheless, whole hospital WGS screening is not yet economical so more judicious uses of pathogen WGS in a confirmatory role have been evaluated. In general, health economic studies have demonstrated favourable cost-effectiveness of WGS compared to standard of care. WGS can lead to reduced transmission and infection rates and lower overall costs⁴⁻⁶. These promising findings pave the way for a budget analysis to be performed to quantify the actual cost outlays required to adopt WGS on a population-wide scale.

Queensland is the second largest and third most populous state in Australia, with a population of over 5 million. The network of public hospitals spans a large geographical area across 16 hospital and health services. For WGS surveillance in infection control to be routinely implemented in publicly funded Queensland Hospitals, a budget impact analysis can assist in resource allocation and

planning. The purpose of this study was to undertake a 5-year budget impact analysis of WGS surveillance using an epidemiological approach.

Methods

Overview

The analysis focused on six MROs: methicillin resistant *Staphylococcus aureus* (MRSA), extended spectrum β -lactamase producing *Escherichia coli* (ESBL *E. coli*), vancomycin-resistant *Enterococcus faecium* (VRE), ESBL-producing *Klebsiella pneumoniae* (ESBL *K. pneumoniae*), carbapenemase-producing *Enterobacter specie* (CPE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB). These organisms were selected because they are subject to hospital outbreaks with serious consequences and accounted for 95% of all sequenced isolates. A review of Australian hospital infection data, government reports and published studies provided the estimates for the analysis. Sequencing data to identify clusters were examined over two years. Costs were aggregated for the state of Queensland based on the expected number of MRO isolates arising in Queensland hospital patients. Costs were calculated annually across five years from the base year 2020. The study was approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (P2353) and the Queensland Government Public Health Act Human Research Ethics Committee (RD007427). The International Society for Pharmacoeconomics and Outcomes Research good-practice guidelines for budget impact analyses provided the framework for this work⁸.

Estimated patients infected with MROs

Each quarter, there are 409,972 hospitalisations in Queensland, and these figures were assumed to be stable over the next five years with full hospital capacity⁹. A recent Australian study showed that the point prevalence of HAIs in Australia was 9.9% of all hospitalisations¹⁰. Using Russo *et al.* (2019) data on 363 HAIs¹⁰, the frequency of organisms detected were: 50 (14%) *S. aureus*, 32 (9%) *E. coli*, 21 (6%) *E. faecium*, 16 (4%) *K. pneumoniae*, 7 (2%) *E. cloacae* and 4 (1%) *A. baumannii*. Although these HAI data were national, and prevalence varied between hospitals, variations were within expected statistical limits to conclude HAIs could reasonably apply to Queensland¹⁰.

For each pathogen, the multidrug resistance rates were based on Wozniak *et al.* (2019), according to site of infection; bloodstream, urinary tract and respiratory tract¹¹, and the Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report¹².

We estimated the total number of Queensland patients colonized or infected (N) for each of the six organisms of interest by Equation 1,

Equation 1.
$$N = \frac{TH \times \%HAIs \times \%Org \times \%MDR}{I/(I + C)}$$

where *TH* is total number of hospitalisations, *HAIs* are healthcare-associated infections, *Org* is the organism of interest, *MDR* is multidrug resistance and the denominator is the infection fraction. The infection fraction, the number of infections to total number of colonisations and infections, was calculated from five years of MRO surveillance data from the Royal Brisbane and Womens’ Hospital (RBWH), Australia (Table 1). The RBWH is the largest public hospital in Australia. Sensitivity analyses were performed on the 95% confidence intervals for each of these separate variables.

Trends in multidrug resistance

Multidrug resistance rates are monitored over time in Australia and differ according to State, type of organism and antimicrobial agents used. For this analysis, annual changes to drug resistance were integrated in the analyses and were 0.3 percentage points for MRSA, 0.009 for ESBL *E. coli*, -2.8 for VRE (decreasing resistance) and 1.0 for ESBL *K. pneumoniae*^{12 13}. No change in resistance rates were used for CPE and CRAB¹².

WGS-surveillance estimates and detection of clusters

Two years of sequencing data outcomes on MROs were available from December 2017 to December 2019. MROs were sequenced at a central facility from 27 hospitals across Queensland. 90% of the 1,783 isolates that were sequenced during the period were from three of the largest Queensland hospitals: RBWH, Queensland Childrens’ Hospital and the Princess Alexandra Hospital. Genetic relatedness was determined by examining the number of core genome single nucleotide polymorphisms (SNP) that differ between any two isolates (pair-wise core genome SNP distance). Genetically related isolates were subdivided into clusters when the SNP distances between then was under a predefined threshold, adjusted for genome size (5 SNPs/mb)^{14 15}. Clustering was evident in all six pathogens and isolates within these clusters demonstrate a high probability that pathogen transmission occurred between patients in the hospital.

Identifying SNP differences, through WGS, to investigate MRO outbreaks has become instrumental in revealing the routes of transmission and guiding the infection control response strategy^{16 17}. The number of isolates in a cluster required to begin a response differs with each MRO. Based on current

clinical practice, a cluster was acted on when two related isolates of an MRO were identified, except for MRSA and ESBL *E. coli* where three related isolates were required. The number of clusters ranged from 2 to 18 across the pathogens with an average number of patients in each cluster ranging from 5 to 13 (Table 1).

Effectiveness of WGS surveillance

The effectiveness of WGS was estimated when clusters were identified and the information was provided to the infection control team, an outbreak was confirmed, and appropriate infection control measures mobilised. The effectiveness of WGS was a factor of the number of isolates that comprise a cluster, the number of clusters identified, and the expected success of intervening to break the chain of transmission. Pathogen transmission is prevented with effective environmental cleaning, patient isolations and contact tracing, which we assume occurs in all cases.

The number of patients that could have prevented being infected or colonized was calculated after WGS identified a cluster (2 or 3 patients) and began control measures. The turnaround time for WGS testing was 7 days; this is the time required for WGS to be processed and results made available to the physicians. For example, if the cluster was identified after 2 patients were detected, and the cluster size was 5 then 3 patients could potentially avoid infection providing 7 days had elapsed between patient 2 and 3 in the cluster (Table 1, Supplementary Figure).

Expected deaths

Data on the frequency of deaths in hospital from patients infected with any of the six MROs were obtained from previous studies¹⁸ and ranged from 6.7% for CPE *E. cloacae* to 36.6% for VRE *E. faecium* (Table 1).

Resource use and costs

Patients who were colonised with an MRO accrued hospital costs for health professional personal protective equipment (PPE), microbiology tests, cleaning and extra infection control nursing time associated with contact precautions. Patients who were infected and showed symptoms accrued these same costs plus costs for antibiotic treatments and bed closures. PPE was valued at \$50 per day for each patient isolated¹⁹. The colonisation and infection mean length of stay for each MRO ranged from 9 to 43 days (Table 2)²⁰⁻²⁵. Published estimates for extra length of stay due to infection were used to calculate the additional hospitalisation costs for each MRO (Table 2)^{21 22 24}. These were valued at \$246 per day¹⁸. Antibiotic treatments were estimated from clinical advice (for infected and

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not colonised patients), and their costs sourced from hospital pharmacy records, the Pharmaceutical Benefit Scheme and published studies ^{11 26 27}. Where necessary, costs were inflated to 2019 prices using the Hospital Pricing Index. Sensitivity analyses were performed on the 95% confidence limits of the values and for treatment costs, $\pm 15\%$.

Analyses

Analyses comprised of aggregated totals of costs for current practice compared with a strategy of WGS surveillance for the six MROs. Analyses were performed in Excel™. Multiway sensitivity analyses were undertaken for each variable (e.g., organism frequency, MRO rate, cluster frequency, infection fraction etc) and high and low values for the six organisms were used simultaneously for each variable. These values were varied within the 95% confidence limits and results were shown for the overall cost difference between current practice (no WGS) and WGS-surveillance (Table 1). A sensitivity analysis was performed on a quicker 4-day turnaround time for WGS testing. Outcomes were reported for the number of expected patients with colonisations and infections, the associated hospitalisation costs and expected deaths.

Patient and Public Involvement

The research study did not involve patient and public involvement.

Results

An estimated 8,003 patients in Queensland hospitals will be infected with one of six common MROs and 89,535 will be colonised, a total of 97,539 patients in the first year. MRSA and VRE made up the majority of the six MROs (Table 3). The expected number of deaths were 2,032 in Year 1. Over five years, the number of patients infected with these MROs decreased by 15% and the number of colonisations decreased by 27% overall, primarily due to decreasing drug resistance for VRE (Table 3).

This compares with a strategy of routine WGS surveillance, with a turnaround time of seven days, where WGS use could avoid 2,085 infected patients and 34,641 colonised patients (Table 4). In total, WGS would avoid 36,726 patients infected/colonised in Year 1 decreasing to 26,984 avoided patient infections/colonisations by Year 5. The number of patient deaths avoided were estimated at 650 in Year 1 to 502 by Year 5 (Table 4).

Total costs for the current management of these colonised and infected patients were an estimated \$170.8 million in Year 1, comprising \$8.0 million for conventional microbiology screening, \$11.9 million for cleaning and nursing time, \$44.8 million for closed-bed days, \$91.1 million for the cost of PPE and \$15.0 million for antibiotic treatments (Table 4).

Compared with a strategy of routine WGS surveillance, sequencing and microbiology costs would be \$26.8 million (\$18.5 million more than standard care), but is offset in the same year by fewer costs for cleaning and nursing, length of stay, PPE and antibiotic treatments (Table 4). The total cost savings were \$30.9 million in Year 1 dropping to \$22.1 million by Year 5. The costs saved for each avoided patient infection was \$6,917 and for each colonization \$475 in Year 1.

The sensitivity analyses showed that when plausible alternative values were used in the analyses, hospital cost savings were always retained, with one exception (Figure 1). The findings were most sensitive to the variation in estimates of preventable patient infections if WGS is undertaken and if this was the lowest value across all six MROs (simultaneously), it would cost an additional \$5.0 million for the WGS strategy. The length of stay for colonisations and organism frequency also changed the base findings by \pm \$10.0 million, but overall cost savings remained.

Discussion

To the best of our knowledge on the incidence of HAIs, MROs and drug resistance rates, nearly 100,000 patients will be infected with potentially serious bacterial infections in Queensland hospitals each year. This will cost the government \$171 million per year to manage. By routinely using WGS to assist infection control teams to manage patients early in bacterial transmission, the expected cost savings are \$30.9 million per year. Not only will hospital costs be saved but thousands of patients will avoid the suffering from infections and the associated risk of death.

Based on the information from WGS, we identified clusters to observe detection patterns of the six MROs among hospital patients. This differs from observing actual transmission among patients because WGS screening was not undertaken on every patient. Retrospectively, we found WGS was performed on between 13-93% of the MROs, with 13% for each of *S.aureus* and *E. coli*, the most common pathogens. The cost savings are heavily influenced by the cluster sizes and potential to avoid infections/colonisations, breaking the chain of transmission. A quicker testing turnaround is

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desirable for infection control processes. When we tested the turnaround time from seven days to four days, we saw only two of the six MROs with notable reductions in patients infected, meaning detections in most patients screened, were greater than a few days between the first two or three patients.

These findings align with other economic studies looking at the benefits of a WGS surveillance-based infection control program. Kumar *et al.* (2020) findings from a single-institute US study, found WGS surveillance to be less costly and more effective than standard of care. Their results were most sensitive to WGS cost and number of isolates sequenced each year⁶. In the UK, Dymond *et al.* (2019) undertook an economic analysis that modelled MRSA genomic surveillance, compared with current practice, and found cost savings for genomic surveillance of ~£730,000 annually to the NHS⁴. And in Australia, our previous work on an ESBL *E. coli* outbreak in a single hospital also predicted significant cost savings and patient outcomes if WGS was implemented early as standard of care and avoided delays in response⁵. The major criticisms of the previous work in this area are the focus on single organisms or single institutions which can limit the generalisability of the findings and studies are retrospective. Our cost analysis somewhat overcomes these issues by analysing data from Queensland hospitals for state-wide application, including six common MROs in our setting, and we estimated future trends based on expected changes in multidrug resistance rates.

The cluster information from WGS was not available in real-time but part of a demonstration project of prospective WGS in response to suspected outbreaks, to detect clusters before they became established as larger outbreaks. The cluster analysis here was performed retrospectively within a research context. Our cost analysis shows the potential for proactive WGS surveillance to support infection control teams under the premise that testing infrastructure, staffing and fast turnaround times are in place on a wider scale. With the extensive COVID-19 pandemic preparations for widespread testing and additional sequencers now in place for Queensland, this would appear possible for more routine whole-genome pathogen sequencing. An additional benefit of the genomic information are the contributions towards phylogenetic libraries and reporting to share knowledge and information with other jurisdictions and the scientific community.

This study should be viewed with some caution as it depends on the accuracy of the estimates used. To deal with the possible uncertainty in the estimates, 95% confidence limits were tested in sensitivity analyses. These found the cost savings were stable despite variation in all but one scenario (i.e. low cluster sizes). Estimating the mean length of stay for infections or colonisations is

difficult to measure and varies significantly depending on MRO type. Colonization length of stay directly influences infection control nursing time and PPE costs and is shown to be a major driver of these findings, with high patient numbers. Further research is necessary to avoid measurement bias of length of stay estimates for HAIs²³. A further issue is the assumption that WGS equipment and infrastructure were available at the outset as these costs are not included in an operational budget impact, but rather, a capital investment. Economies of scale with wider testing and lower testing may be seen the sensitivity analyses covering a lower unit cost for WGS. Overall, we suggest the findings are conservative because WGS testing was only used infrequently as a total percentage of MRO isolates and if screening were higher, more infections and therefore higher cluster sizes would be apparent (at reasonable cost). The expected consequences of a WGS strategy is also likely to be conservative and other MROs were excluded in the analysis. Furthermore, it is possible that an organism can contribute to more than one type of HAI and therefore, that the impacts of prevention may also be greater.

Conclusion

The proactive use of WGS surveillance for infection control of common MROs was estimated to be cost saving for hospitals and beneficial for patients. This study has implications for government resource allocation decisions and establishes a favourable value proposition for adopting pathogen WGS into routine clinical practice in Queensland.

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Author contributions

LG & TE conceived the study aim and purpose. TE undertook the main analyses with assistance from LG. BF, PR, DP, BM provided data for this study, critically reviewed the study, contributed to drafting the paper and provided subject matter expertise. PH, DP & BF provided clinical and scientific expertise. All authors contributed to drafting the manuscript and reviewed the final version.

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Competing Interests Statement

The authors have no conflicts of interest to declare. All authors to please confirm.

Data sharing statement

The Excel worksheet and analysis file are available upon request to the authors.

Figure Legends

Figure 1: Tornado diagram of change in the main analysis cost savings AU\$30.9 million, with higher and lower input values

Note: HAIs – hospital-associated infections, WGS – whole-genome sequencing, PPE – personal protective equipment.

Supplementary Figure: Illustration of clusters and avoidable infections

References

1. Mitchell BG, Shaban RZ, MacBeth D, et al. The burden of healthcare-associated infection in Australian hospitals: A systematic review of the literature. *Infect Dis Health* 2017;22(3):117-28. doi: 10.1016/j.idh.2017.07.001. Epub 17 Aug 15.
2. Australian Institute of Health and Welfare (AIHW). General Record of Incidence of Mortality (GRIM) data, Cat. no: PHE 229, Canberra: AIHW; 2019 [Available from: <https://www.aihw.gov.au/reports/life-expectancy-deaths/grim-books> accessed 3/6/2020 2020.
3. Li LM, Grassly NC, Fraser C. Genomic analysis of emerging pathogens: methods, application and future trends. *Genome biology* 2014;15(11):541. doi: 10.1186/s13059-014-0541-9 [published Online First: 2014/11/25]
4. Dymond A, Davies H, Mealing S, et al. Genomic surveillance of methicillin-resistant *Staphylococcus aureus*: a mathematical early modelling study of cost effectiveness. *Clinical Infectious Diseases* 2019:ciz480. doi: 10.1093/cid/ciz480
5. Elliott TM, Lee XJ, Foeglein A, et al. A hybrid simulation model approach to examine bacterial genome sequencing during a hospital outbreak. *BMC Infect Dis* 2020;20(1):72. doi: 10.1186/s12879-019-4743-3.
6. Kumar P, Sundermann AJ, Martin EM, et al. Method for economic evaluation of bacterial whole genome sequencing surveillance compared to standard of care in detecting hospital outbreaks. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2020 doi: 10.1093/cid/ciaa512 [published Online First: 2020/05/06]
7. Gordon LG, White NM, Elliott TM, et al. Estimating the cost of genomic sequencing in cancer control. *BMC Health Services Research* 2020;DOI: 10.1186/s12913-020-05318-y
8. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value in Health* 2014;17(1):5-14. doi: <https://doi.org/10.1016/j.jval.2013.08.2291>
9. Health Q. Quarterly hospital activity information for October, November, December 2019: Queensland government; [cited 2020 24/04/2020]. Available from: <http://www.performance.health.qld.gov.au/Hospital/HospitalActivity/99999>.
10. Russo PL, Stewardson AJ, Cheng AC, et al. The prevalence of healthcare associated infections among adult inpatients at nineteen large Australian acute-care public hospitals: A point prevalence survey. *Antimicrobial Resistance and Infection Control* 2019;8(1) doi: 10.1186/s13756-019-0570-y
11. Wozniak TM, Bailey EJ, Graves N. Health and economic burden of antimicrobial-resistant infections in Australian hospitals: A population-based model. *Infection Control and Hospital Epidemiology* 2019;40(3):320-27. doi: 10.1017/ice.2019.2
12. Coombs G BJ, Daley D, Collignon P, Cooley L, Gottlieb T, Iredell J, Kotsanas D, Nimmo G and Robson J on behalf of the Australian Group on Antimicrobial Resistance and Australian Commission on Safety and Quality in Health Care. Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report. Sydney: Australian Commission on Safety and Quality in Health Care, 2019.
13. Care ACoSaQIH. Australian Passive Antimicrobial Resistance Surveillance. First report: multi-resistant organisms. Sydney:: ACSQHC, 2018.
14. Octavia S, Wang Q, Tanaka MM, et al. Delineating community outbreaks of *Salmonella enterica* serovar Typhimurium by use of whole-genome sequencing: insights into genomic variability within an outbreak. *J Clin Microbiol* 2015;53(4):1063-71. doi: 10.128/JCM.03235-14. Epub 2015 Jan 21.
15. Stinear TP, Holt KE, Chua K, et al. Adaptive change inferred from genomic population analysis of the ST93 epidemic clone of community-associated methicillin-resistant *Staphylococcus aureus*. *Genome Biol Evol* 2014;6(2):366-78. doi: 10.1093/gbe/evu022.

16. Chapman P, Forde BM, Roberts LW, et al. Genomic Investigation Reveals Contaminated Detergent as the Source of an Extended-Spectrum- β -Lactamase-Producing *Klebsiella michiganensis* Outbreak in a Neonatal Unit. *Journal of clinical microbiology* 2020;58(5) doi: 10.1128/jcm.01980-19 [published Online First: 2020/02/28]

17. Roberts LW, Harris PNA, Forde BM, et al. Integrating multiple genomic technologies to investigate an outbreak of carbapenemase-producing *Enterobacter hormaechei*. *Nature communications* 2020;11(1):466. doi: 10.1038/s41467-019-14139-5 [published Online First: 2020/01/26]

18. Page K, Barnett AG, Graves N. What is a hospital bed day worth? A contingent valuation study of hospital Chief Executive Officers. *BMC health services research* 2017;17(1):137-37. doi: 10.1186/s12913-017-2079-5

19. Otter JA, Burgess P, Davies F, et al. Counting the cost of an outbreak of carbapenemase-producing Enterobacteriaceae: an economic evaluation from a hospital perspective. *Clinical Microbiology and Infection* 2017;23(3):188-96. doi: <https://doi.org/10.1016/j.cmi.2016.10.005>

20. Álvarez-Marín R, López-Rojas R, Márquez JA, et al. Colistin dosage without loading dose is efficacious when treating carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia caused by strains with high susceptibility to colistin. *PLoS ONE* 2016;11(12) doi: 10.1371/journal.pone.0168468

21. Kirwin E, Varughese M, Waldner D, et al. Comparing methods to estimate incremental inpatient costs and length of stay due to methicillin-resistant *Staphylococcus aureus* in Alberta, Canada. *BMC Health Services Research* 2019;19(1) doi: 10.1186/s12913-019-4578-z

22. Lloyd-Smith P, Younger J, Lloyd-Smith E, et al. Economic analysis of vancomycin-resistant enterococci at a Canadian hospital: assessing attributable cost and length of stay. *The Journal of hospital infection* 2013;85(1):54-9. doi: 10.1016/j.jhin.2013.06.016 [published Online First: 2013/08/08]

23. Rodriguez-Acevedo AJ, Lee XJ, Elliot TM, et al. Hospitalization costs for patients colonized with carbapenemase-producing Enterobacterales during an Australian outbreak. *Journal of Hospital Infection* 2020 doi: <https://doi.org/10.1016/j.jhin.2020.03.009>

24. Suzuki H, Perencevich EN, Nair R, et al. Excess length of acute inpatient stay attributable to acquisition of hospital-onset Gram-negative bloodstream infection with and without antibiotic resistance: a multistate model analysis. *Antibiotics* 2020;9(2) doi: 10.3390/antibiotics9020096

25. Zhen X, Lundborg CS, Sun X, et al. The Clinical and Economic Impact of Antibiotic Resistance in China: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)* 2019;8(3):115. doi: 10.3390/antibiotics8030115

26. Health SA. *Staphylococcus aureus* Bacteraemia (SAB) Management Clinical Guideline. Government of South Australia, 2019.

27. Network PI. GUIDANCE ON TREATMENT OF CARBAPENAMASE PRODUCING ENTEROBACTERIACEAE UK Clinical Pharmacy Association 2016 [Available from: <https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/UKCPA%20CPE%20Guidance.pdf> accessed 16/04/2020.

Table 1: Parameters values used in estimating the number of hospitalised patients affected by MROs

Variable	Estimate (95%CI)	Source
No. Queensland hospital admissions per quarter	409,972 (348,476, 462,243)	Queensland Health (1)
Prevalence of all hospitalisations with a HAI	9.9% (8.8%, 11.0%)	Russo (2019)(2)
% of species of all HAIs ^a		
<i>Staphylococcus aureus</i>	13.8% (10.2%, 17.3%)	Russo (2019)(2)
<i>Escherichia coli</i>	8.8% (5.9%, 11.7%)	
<i>Enterococcus faecium</i>	5.8% (3.4%, 8.2%)	
<i>Klebsiella pneumoniae</i>	4.4% (2.3%, 6.5%)	
<i>Enterobacter cloacae</i>	1.9% (0.5%, 3.3%)	
<i>Acinetobacter baumannii</i>	1.1% (0.0%, 2.2%)	
% multidrug resistant ^b		
MRSA	14.4% (13.3%, 17.2%)	Wozniak (2019)(3)
ESBL <i>E. coli</i>	5.3% (4.5%, 6.5%)	
VRE	37.8% (26.7%, 49.2%)	
ESBL <i>K. pneumoniae</i>	4.1% (3.6%, 7.7%)	Coombs (2018)(4)
CPE	4.1% (3.9%, 4.3%)	
CR-Ab	3.2% (2.7%, 3.7%)	
Annual change of species incidence (% points)		
MRSA	0.3	ACSQHC (5)
ESBL <i>E. coli</i>	0.9	
VRE	-2.8	
ESBL <i>K. pneumoniae</i>	1.0	Coombs (2018)(4)
CPE	0.0	
CR-Ab	0.0	
Infection fraction of total infected+colonised patients		
MRSA	20.6% (18.6%, 22.5%)	Hospital / Clinical Data
ESBL <i>E. coli</i>	30.0% (23.9%, 36.1%)	
VRE	4.6% (2.9%, 6.3%)	
ESBL <i>K. pneumoniae</i>	27.6% (21.1%, 34.0%)	
CPE	35.9% (20.8%, 51.0%)	
CR-Ab	15.2% (4.8%, 25.6%)	
Cluster frequency and decreased cluster size (95%CI)		
MRSA ^c	0.02, 5.38 (1.37, 9.38)	Sequencing data records
ESBL <i>E. coli</i> ^c	0.02, 10.25 (2.94, 17.56)	
VRE	0.05, 8.29 (3.89, 12.68)	
ESBL <i>K. pneumoniae</i>	0.02, 3.25 (1.23, 5.27)	
CPE	0.06, 6.33 (-1.20 ^d , 13.87)	
CR-Ab	0.06, 4.00 (-1.88 ^d , 9.88)	

Note: HAI – Hospital acquired infection, CI – confidence interval, MRO – Multidrug resistant organism, MRSA – Methicillin-resistant - staphylococcus aureus, ESBL - Extended spectrum beta-lactamases, VRE - Vancomycin-resistant Enterococci, CPE - Carbapenemase-Producing Enterobacteriaceae, CR - carbapenem-resistant, Ab - Acinetobacter baumannii,

^a The HAI percentage of each organism, denominator is total HAIs.

^b Denominator is the total number of the organism detected.

^c Infection control response required cluster size of 3 isolates before action is taken.

^d The negative number does not denote an increase in isolates. Two isolates are required to identify the cluster, so this negative value means that no clusters are identified.

Table 2: Variables used in estimating the cost of MRO screening and treatments

Variable	Estimate (95%CI)	Comment/ Source
Cost of screening for pathogens		
Usual screening - Microbiology test and PCR	\$82 (\$58, \$107)	Elliott (2020) (6)
WGS - Microbiology test, PCR and WGS	\$437 (\$309, \$565)	Elliott (2020) (6)
Cleaning and extra nurse time per detection ^a	\$122 (\$90, \$155)	Elliott (2020) (6)
PPE per day in isolation	\$50 (\$35, \$65)	Otter (2016)(7)
Closed-bed day	\$246 (\$151, \$342)	Page (2017)(8)*
Cost of antibiotic treatment per infected patient		
MRSA (Vancomycin) ^b	\$580 (\$409, \$750)	SA guideline (9) / Hospital Pharm
ESBL <i>E Coli</i> . (Meropenem) ^c	\$321 (\$227, \$416)	Wozniak (2018)(10) and Hospital
VRE (Linezolid & Daptomycin) ^d	\$3,433, (\$2,424, \$4,443)	Pharmacy pricing
CPE (Colistin + Meropenem ^e & Gentamicin/Amikacin ^f)	\$2,920, (\$2,061, \$3,778)	Pharmacy infection network(11) and Hospital Pharmacy pricing
CR-Ab (Colistin + tigecycline ^g & Colistin + Meropenem ^e)	\$3,199 (\$2,258, \$4,139)	Viehman (2014) (12) and Hospital Pharmacy pricing
MRSA		
Colonization LOS	29.2 (16.4, 51.9)	Kirwin (2019)(13)
Infection LOS	42.7 (23.6, 77.2)	Kirwin (2019)(13)
ESBL <i>E coli</i>		
Colonization LOS	16.0 (8.0, 31.0)	Suzuki (2020)(14)
Infection LOS	33.0 (18.0, 64.0)	Suzuki (2020)(14)
VRE		
Colonisation LOS	15.0 (9.0, 30.0)	Tan (2018) (15)
Infection LOS	34.0 (29.6, 38.4)	Lloyd-smith (2013)(16)
ESBL <i>K. pneumoniae</i>		
Colonisation LOS	16.0 (8.0, 31.0)	Suzuki (2020)(14)
Infection LOS	33.0 (18.0, 64.0)	Suzuki (2020)(14)
CPE		
Colonisation LOS	12.0 (3.0, 21.0)	Rodriguez-Acevedo (2020)(17)*
Infection LOS	29.0 (22.7, 35.3)	Zhen (2019) (18)
CR-Ab		
Colonisation LOS	9.0 (6.0, 22.0)	A' lvarez-Mari'n 2016(19)
Infection LOS	21.5 (11.5, 42.8)	A' lvarez-Mari'n 2016(19)
Closed bed days^h		
MRSA	35.2 (16.3, 69.4)	Kirwin (2019)(13)
ESBL <i>E coli</i>	16.6 (3.6, 30.4)	Suzuki (2020)(14)
VRE	13.8 (10.0, 16.9)	Lloyd-smith (2013)(16)
ESBL <i>K pneumoniae</i>	16.6 (3.6, 30.4)	Suzuki (2020)(14)
CPE	14.5 (11.4, 17.6)	Assumption ⁱ
CR-Ab	10.8 (5.8, 21.4)	Assumption ⁱ

Note: CI – confidence interval, WGS – whole genome sequencing, LOS – length of stay, PPE – personal protective equipment, MRSA – Methicillin-resistant staphylococcus aureus, ESBL - Extended spectrum beta-lactamases, VRE - Vancomycin-resistant Enterococci, CPE - Carbapenemase-Producing Enterobacteriaceae, CR-Ab - Carbapenem-resistant *Acinetobacter baumannii*,

*Australian study/data

^a Cleaning is for decontamination of the room and Nursing time is for isolating patient, contact precautions, etc

^b Flucloxacillin administered at 2g IV 6 hourly initially and Vancomycin at 2g

^c Meropenem administered at 1.0-2g for 3 times daily

^d Linezolid administered at 2x0.6 g for 14 days and Daptomycin 0.6g daily

^e Colistin administered at 275mg for 14 days and Meropenem administered at 1.0-2g for 3 times daily

^f Gentamicin administered at 5-7mg/kg for 14 days and Amikacin administered at 15mg/kg

^g Colistin administered at 275mg for 14 days and tigecycline administered at 100mg followed by 50mg every 12 hours

^h Closed bed days was estimated by the excess LOS for infections by each specie.

ⁱ Extra LOS was assumed to be 50% of the infection LOS

Table 3: Estimated number of Queensland patients with multidrug resistant organisms and deaths from sepsis

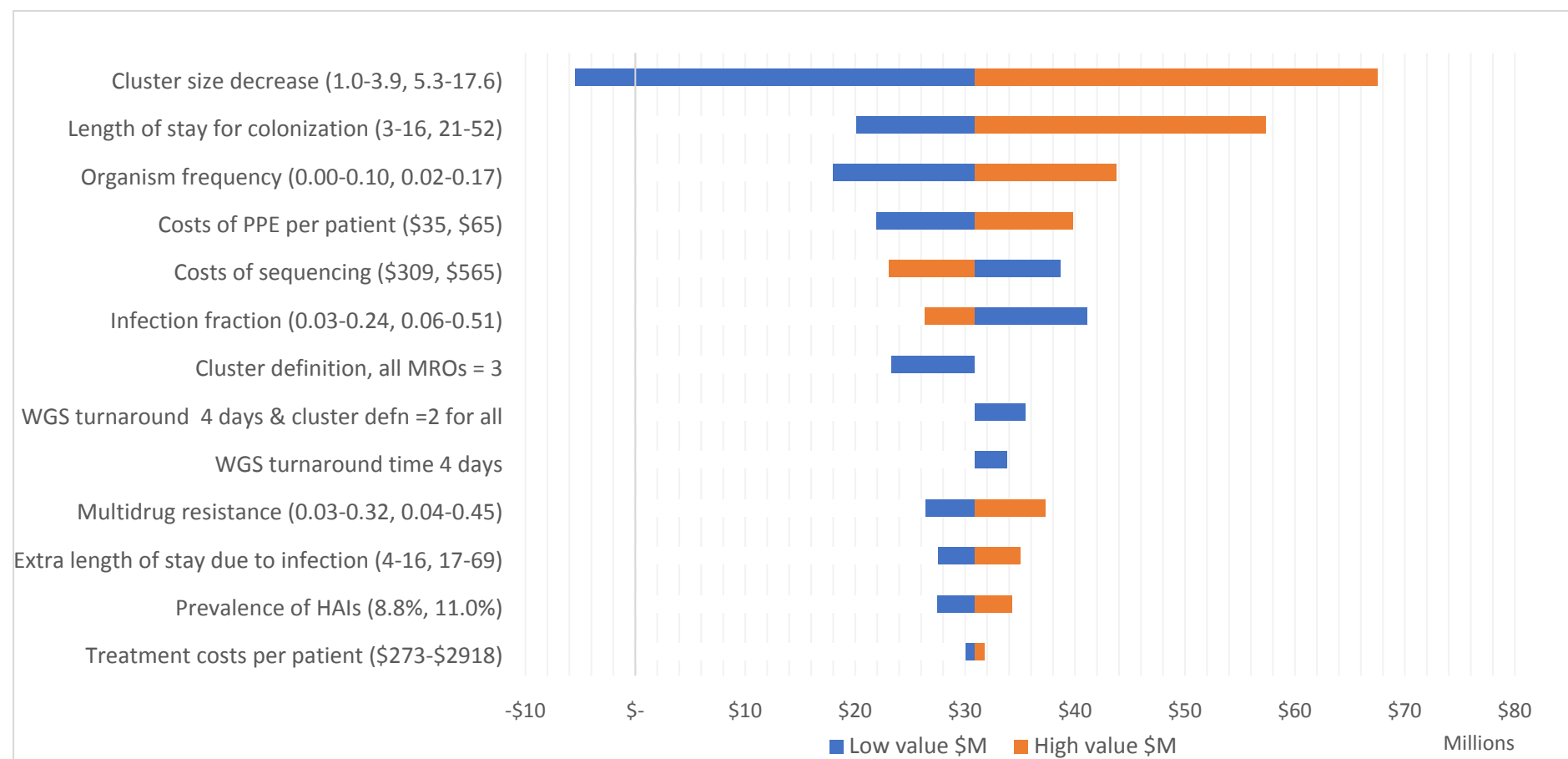
	2020	2021	2022	2023	2024
No. annual hospitalisations	1,639,888	1,639,888	1,639,888	1,639,888	1,639,888
No. HAIs	162,349	162,349	162,349	162,349	162,349
No. HAIs from MROs of interest	58,141	58,141	58,141	58,141	58,141
No. patients infected with drug resistant MROs ¹					
MRSA	3,223	3,290	3,357	3,424	3,491
ESBL <i>E. coli</i>	752	881	1,009	1,138	1,267
VRE	3,551	3,288	3,025	2,762	2,499
ESBL <i>K. pneumoniae</i>	292	364	435	507	578
CPE	128	128	128	128	128
CR-Ab	57	57	57	57	57
Total drug resistant MROs of concern	8,003	8,008	8,012	8,017	8,021
Total no. pts colonised with drug resistant MROs	89,536	84,801	80,067	75,332	70,598
Total no. pts expected with infections/colonisations	97,539	92,809	88,079	83,349	78,619
Deaths from sepsis	2032	1982	1932	1881	1831

Note: HAI – Healthcare-associated infection, MRO – Multidrug resistant organism, MRSA – Methicillin-resistant *Staphylococcus aureus*, ESBL - Extended spectrum β -lactamases, VRE - Vancomycin-resistant Enterococci, CPE - Carbapenemase-producing enterobacteriaceae, CR - carbapenem-resistant, Ab - *Acinetobacter baumannii*,
 1. Adjusted for change in drug resistance rate.

Table 4: Estimated differences in costs AU\$ and patient deaths of current practice versus WGS surveillance

	2020	2021	2022	2023	2024
CURRENT PRACTICE					
Total no. pts expected to have MRO infections/colonis	97,539	92,809	88,079	83,349	78,619
Cost of microbiology screening	\$ 8,028,283	\$ 7,638,967	\$ 7,249,651	\$ 6,860,335	\$ 6,471,019
Cost of cleaning and nursing time	\$ 11,911,230	\$ 11,333,618	\$ 10,756,006	\$ 10,178,394	\$ 9,600,782
Cost of extra length of stay	\$ 44,793,430	\$ 45,297,162	\$ 45,800,893	\$ 46,304,625	\$ 46,808,356
Cost of PPE	\$ 91,162,386	\$ 87,836,074	\$ 84,509,762	\$ 81,183,450	\$ 77,857,139
Cost of antibiotic treatment of patients	\$ 14,952,034	\$ 14,152,425	\$ 13,352,816	\$ 12,553,207	\$ 11,753,598
Total Cost - CURRENT PRACTICE	\$ 170,847,364	\$ 166,258,246	\$ 161,669,129	\$ 157,080,012	\$ 152,490,895
Expected no. patient deaths	2032	1982	1932	1881	1831
WGS SURVEILLANCE					
Total no. potentially avoided infections with WGS (pts)	2085	2003	1921	1839	1757
Total no. potentially avoided colonisations with WGS (pts)	34641	32287	29934	27580	25227
Total no. potentially avoided infected/colonised with WGS	36726	34290	31855	29419	26984
Cost of WGS	\$ 26,575,746	\$ 25,573,072	\$ 24,570,397	\$ 23,567,723	\$ 22,565,049
Cost of cleaning and nursing time	\$ 7,426,340	\$ 7,146,152	\$ 6,865,964	\$ 6,585,777	\$ 6,305,589
Cost of extra length of stay	\$ 36,149,780	\$ 36,881,764	\$ 37,613,748	\$ 38,345,732	\$ 39,077,716
Cost of PPE	\$ 60,703,607	\$ 59,267,592	\$ 57,831,577	\$ 56,395,563	\$ 54,959,548
Cost of treating infected patients	\$ 9,123,437	\$ 8,713,828	\$ 8,304,219	\$ 7,894,610	\$ 7,485,001
Total Cost - WGS Surveillance	\$ 139,978,910	\$ 137,582,408	\$ 135,185,906	\$ 132,789,404	\$ 130,392,902
Expected no. patient deaths	1382	1369	1356	1342	1329
Cost savings with WGS Surveillance	\$ 30,868,454	\$ 28,675,839	\$ 26,483,223	\$ 24,290,608	\$ 22,097,992
Patient deaths avoided	650	613	576	539	502
Costs saved per avoided infection	-\$ 14,805	-\$ 14,317	-\$ 13,787	-\$ 13,210	-\$ 12,579
Costs saved per avoided colonisation	-\$ 891	-\$ 888	-\$ 885	-\$ 881	-\$ 876

Figure 1: Tornado diagram of change in the main analysis cost savings AU\$30.9 million, with higher and lower input values



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1. Health Q. Quarterly hospital activity information for October, November, December 2019: Queensland government; [cited 2020 24/04/2020]. Available from: <http://www.performance.health.qld.gov.au/Hospital/HospitalActivity/99999>.

2. Russo PL, Stewardson AJ, Cheng AC, Bucknall T, Mitchell BG. The prevalence of healthcare associated infections among adult inpatients at nineteen large Australian acute-care public hospitals: A point prevalence survey. *Antimicrobial Resistance and Infection Control*. 2019;8(1).

3. Wozniak TM, Bailey EJ, Graves N. Health and economic burden of antimicrobial-resistant infections in Australian hospitals: A population-based model. *Infection Control and Hospital Epidemiology*. 2019;40(3):320-7.

4. Coombs G BJ, Daley D, Collignon P, Cooley L, Gottlieb T, Iredell J, Kotsanas D, Nimmo G and Robson J on behalf of the Australian Group on Antimicrobial Resistance and Australian Commission on Safety and Quality in Health Care. Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report. Sydney: Australian Commission on Safety and Quality in Health Care; 2019.

5. Care ACoSaQiH. Australian Passive Antimicrobial Resistance Surveillance. First report: multi-resistant organisms. Sydney:: ACSQHC; 2018.

6. Elliott TM, Lee XJ, Foeglein A, Harris PN, Gordon LG. A hybrid simulation model approach to examine bacterial genome sequencing during a hospital outbreak. *BMC Infect Dis*. 2020;20(1):72. doi: 10.1186/s12879-019-4743-3.

7. Otter JA, Burgess P, Davies F, Mookerjee S, Singleton J, Gilchrist M, et al. Counting the cost of an outbreak of carbapenemase-producing Enterobacteriaceae: an economic evaluation from a hospital perspective. *Clinical Microbiology and Infection*. 2017;23(3):188-96.

8. Page K, Barnett AG, Graves N. What is a hospital bed day worth? A contingent valuation study of hospital Chief Executive Officers. *BMC health services research*. 2017;17(1):137-.

9. Health SA. Staphylococcus aureus Bacteraemia (SAB) Management Clinical Guideline. Government of South Australia 2019.

10. Wozniak TM. Clinical management of drug-resistant bacteria in Australian hospitals: An online survey of doctors' opinions. *Infection, Disease & Health*. 2018;23(1):41-8.

11. Network PI. GUIDANCE ON TREATMENT OF CARBAPENAMASE PRODUCING ENTEROBACTERIACEAE UK Clinical Pharmacy Association 2016 [Available from: <https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/UKCPA%20CPE%20Guidance.pdf>].

12. Viehman JA, Nguyen MH, Doi Y. Treatment options for carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii* infections. *Drugs*. 2014;74(12):1315-33.

13. Kirwin E, Varughese M, Waldner D, Simmonds K, Joffe AM, Smith S. Comparing methods to estimate incremental inpatient costs and length of stay due to methicillin-resistant *Staphylococcus aureus* in Alberta, Canada. *BMC Health Services Research*. 2019;19(1).

14. Suzuki H, Perencevich EN, Nair R, Livorsi DJ, Goto M. Excess length of acute inpatient stay attributable to acquisition of hospital-onset Gram-negative bloodstream infection with and without antibiotic resistance: a multistate model analysis. *Antibiotics*. 2020;9(2).

15. Tan D, Htun HL, Koh J, Kanagasabai K, Lim J-W, Hon P-Y, et al. Comparative Epidemiology of Vancomycin-Resistant Enterococci Colonization in an Acute-Care Hospital and Its Affiliated Intermediate- and Long-Term Care Facilities in Singapore. *Antimicrobial Agents and Chemotherapy*. 2018;62(12):e01507-18.

16. Lloyd-Smith P, Younger J, Lloyd-Smith E, Green H, Leung V, Romney MG. Economic analysis of vancomycin-resistant enterococci at a Canadian hospital: assessing attributable cost and length of stay. *The Journal of hospital infection*. 2013;85(1):54-9.
17. Rodriguez-Acevedo AJ, Lee XJ, Elliot TM, Gordon LG. Hospitalization costs for patients colonized with carbapenemase-producing Enterobacterales during an Australian outbreak. *Journal of Hospital Infection*. 2020.
18. Zhen X, Lundborg CS, Sun X, Hu X, Dong H. The Clinical and Economic Impact of Antibiotic Resistance in China: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)*. 2019;8(3):115.
19. Álvarez-Marín R, López-Rojas R, Márquez JA, Gómez MJ, Molina J, Cisneros JM, et al. Colistin dosage without loading dose is efficacious when treating carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia caused by strains with high susceptibility to colistin. *PLoS ONE*. 2016;11(12).

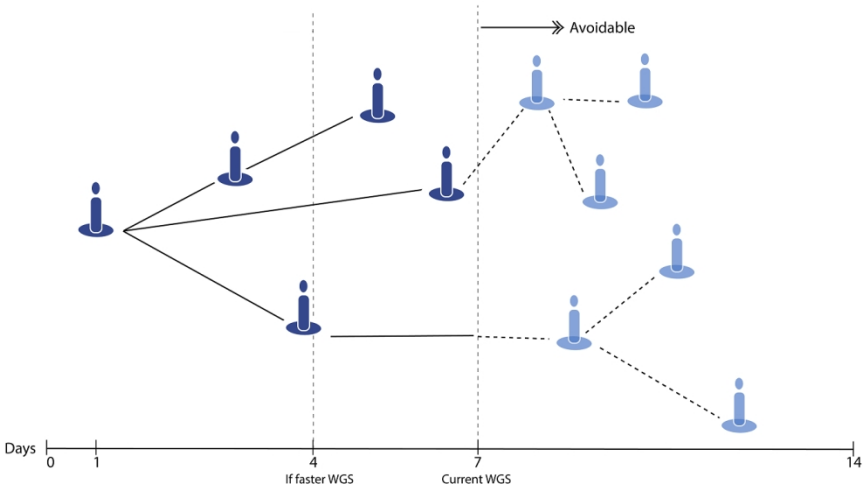


Illustration of clusters and avoidable infections

BMJ Open

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Budget impact analysis of routinely using whole-genomic sequencing of six multidrug-resistant bacterial pathogens in Queensland, Australia

Louisa G. Gordon^{1,2,3}, Thomas M. Elliott¹, Brian Forde^{4,5}, Brett G. Mitchell⁶, Philip L. Russo⁷, David L. Paterson⁵, Patrick N.A. Harris^{5,8}

Affiliations:

1. QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
2. School of Nursing, Queensland University of Technology, Brisbane, Queensland, Australia.
3. School of Population Health, The University of Queensland, Brisbane, Queensland, Australia
4. School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, Australia
5. The University of Queensland, Centre for Clinical Research, Brisbane, Queensland, Australia
6. School of Nursing and Midwifery, The University of Newcastle, Newcastle, NSW, Australia
7. School of Nursing and Midwifery, Monash University, Melbourne, Australia
8. Pathology Queensland, Queensland Health, Brisbane, Queensland, Australia

Correspondence to: Louisa Gordon, QIMR Berghofer Medical Research Institute, Population Health Department, Locked Bag 2000, Royal Brisbane Hospital, Herston, Brisbane, Australia Ph:61-7-3845 3717 Fx:61-7-3845 3502
louisa.gordon@qimrberghofer.edu.au

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Abstract

Objective: To predict the effects of routine use of whole-genome sequencing (WGS) of bacterial pathogens on healthcare costs and compare with the corresponding effects of standard of care.

Design: Budget impact analysis over the following 5 years. Data were primarily from sequencing results on clusters of multidrug-resistant organisms across 27 hospitals. Model inputs were derived from hospitalisation and sequencing data, epidemiological and costing reports, and included multidrug resistance rates and their trends.

Setting: Queensland, Australia

Participants: Hospitalised patients.

Interventions: WGS surveillance of six common multidrug-resistant organisms (*Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Enterobacter* sp. and *Acinetobacter baumannii*) compared with standard of care or routine microbiology testing.

Primary and secondary outcomes: Expected hospital costs, counts of patient infections and colonisations, deaths from bloodstream infections.

Results: In 2021, 97,539 patients in Queensland are expected to be infected or colonised with one of six multidrug-resistant organisms with standard of care testing. A strategy of WGS surveillance and earlier infection control measures could avoid 36,726 infected or colonised patients and avoid 650 deaths. Total costs under standard of care were AU\$170.8 million in 2021. WGS surveillance cost an additional AU\$26.8 million but was offset by fewer costs for cleaning, nursing, personal protective equipment, shorter hospital stays and antimicrobials to produce overall cost savings of \$30.9 million in 2021. Sensitivity analyses showed cost savings remained when input values were varied at 95% confidence limits.

Conclusions: Compared with standard of care, WGS surveillance at a statewide level could prevent substantial numbers of hospital patients infected with multidrug resistant organisms, related deaths and save healthcare costs. Primary prevention through routine use of WGS is an investment priority for the control of serious hospital-associated infections.

Key words: whole-genome sequencing, pathogen genomics, healthcare-associated infections, budget impact analysis, cost analysis

Word count (main text): 2766

Article Summary

Strengths and Limitations of this study

- To the best of our knowledge, this is the first study to assess the projected budget impact for a local government to invest in routine whole-genome sequencing of serious bacterial pathogens to assist hospital infection control teams.
- Analyses relied on recent outcomes from sequencing data to identify clusters, hospitalisation data, prevalence of healthcare-associated infections, and detailed costing of all hospital resources while sensitivity analyses assessed variation in inputs and the stability of the results.
- Projected cost savings of a whole genome sequencing strategy relies on the success of infection control teams to act decisively and effectively on the information of patient clusters.

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Introduction

Healthcare-associated infections (HAIs) are the most common complications in hospitalised patients in Australia¹. The associated economic burden is enormous resulting in longer hospital stays, higher treatment costs and in severe cases, intensive care unit stays and bed closures. Rates of bacterial infections causing septicaemia and deaths rose from the 1980s but has stabilised since 2000². Consequently, substantial resources are devoted to controlling HAIs, especially for multidrug resistant organisms (MROs), with strict infection control practices operating in most hospitals.

Whole-genome sequencing (WGS) of pathogens can identify genetically related isolates and identify patients involved in an outbreak. WGS can confirm or refute suspected related cases of infectious pathogens, discriminate between different strains, and classify novel pathogens³. By detecting different strains with varied transmissibility, patients can be better managed by the infection control team. Currently, usual laboratory tests to confirm infectious pathogens do not provide this granular information on different strains. Through WGS, multiple isolates can be analysed together to uncover the evolution of the pathogen (phylogenetics) and transmission history (who infected whom). In the future, sequencing is expected to identify information about resistance to certain antibiotics which has potential to guide antibiotic treatment.

There is an emerging body of work on the economic value of WGS surveillance in hospital practice⁴⁻⁶. While WGS of human tissue can be expensive⁷, bacterial and viral genomes are less complex and the sequencing cost is less than one-tenth that for a human genome⁵. Nevertheless, whole hospital WGS screening is not yet economical so more judicious uses of pathogen WGS in a confirmatory role have been evaluated. In general, health economic studies have demonstrated favourable cost-effectiveness of WGS compared to standard of care. WGS can lead to reduced transmission and infection rates and lower overall costs⁴⁻⁶. These promising findings pave the way for a budget analysis to be performed to quantify the actual cost outlays required to adopt WGS on a population-wide scale.

Queensland is the second largest and third most populous state in Australia, with a population of over 5 million. The network of public hospitals spans a large geographical area across 16 hospital and health services. For WGS surveillance in infection control to be routinely implemented in publicly funded Queensland Hospitals, a budget impact analysis can assist in resource allocation and planning. The purpose of this study was to undertake a 5-year budget impact analysis of WGS

surveillance compared with standard care using an epidemiological approach from the state government perspective.

Methods

Overview

The analysis focused on six MROs: methicillin resistant *Staphylococcus aureus* (MRSA), extended spectrum β -lactamase producing *Escherichia coli* (ESBL *E. coli*), vancomycin-resistant *Enterococcus faecium* (VRE), ESBL-producing *Klebsiella pneumoniae* (ESBL *K. pneumoniae*), carbapenemase-producing *Enterobacteriales* (CPE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB). These organisms were selected because they are subject to hospital outbreaks with serious consequences and accounted for 95% of all sequenced isolates. A review of Australian hospital infection data, government reports and published studies provided the estimates for the analysis. Sequencing data to identify clusters were examined over two years. Costs were aggregated for the state of Queensland based on the expected number of MRO isolates arising in Queensland hospital patients. Costs were calculated annually across five years from the base year 2020. The study was approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (P2353) and the Queensland Government Public Health Act Human Research Ethics Committee (RD007427). The International Society for Pharmacoeconomics and Outcomes Research good-practice guidelines for budget impact analyses provided the framework for this work⁸.

Estimated patients infected with MROs

Each quarter, there are 409,972 hospitalisations in Queensland, and these figures were assumed to be stable over the next five years with full hospital capacity⁹. A recent Australian study showed that the point prevalence of HAIs in Australia was 9.9% of all hospitalisations¹⁰. Using Russo *et al.* (2019) data on 363 HAIs¹⁰, the frequency of organisms detected were: 50 (14%) *S. aureus*, 32 (9%) *E. coli*, 21 (6%) *E. faecium*, 16 (4%) *K. pneumoniae*, 7 (2%) *E. cloacae* and 4 (1%) *A. baumannii* (with 216 (62%) other organisms making up the remainder). Although these HAI data were national, and prevalence varied between hospitals, variations were within expected statistical limits to conclude HAIs could reasonably apply to Queensland¹⁰.

For each pathogen, the multidrug resistance rates were based on Wozniak *et al.* (2019), according to site of infection; bloodstream, urinary tract and respiratory tract¹¹, and the Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report¹².

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We estimated the total number of Queensland patients colonized or infected (N) for each of the six organisms of interest by Equation 1,

Equation 1.
$$N = \frac{TH \times \%HAIs \times \%Org \times \%MDR}{I/(I + C)}$$

where *TH* is total number of hospitalisations, *HAIs* are healthcare-associated infections, *Org* is the organism of interest, *MDR* is multidrug resistance and the denominator is the infection fraction ($I/(I+C)$). The infection fraction is the number of infections as a fraction of the total number of colonisations and infections. This is required on the denominator to increase the N and account for colonisations AND infections as the true burden of HAI numbers. The infection fraction was calculated from five years of MRO surveillance data from the Royal Brisbane and Womens’ Hospital (RBWH), Australia (Table 1). The RBWH is the largest public hospital in Australia. Sensitivity analyses were performed on the 95% confidence intervals for each of these separate variables.

Trends in multidrug resistance

Multidrug resistance rates are monitored over time in Australia and differ according to State, type of organism and antimicrobial agents used. For this analysis, annual changes to drug resistance were integrated in the analyses and were 0.3 percentage points for MRSA, 0.009 for ESBL *E. coli*, -2.8 for VRE (decreasing resistance) and 1.0 for ESBL *K. pneumoniae*^{12 13}. No change in resistance rates were used for CPE and CRAB¹².

WGS-surveillance estimates and detection of clusters

Data from isolates that were sequenced came from a research demonstration project of prospective WGS for isolates of suspected outbreaks, to detect clusters before they became established as larger outbreaks. The routine use of WGS for widespread adoption would also be in this context and not for indiscriminate testing. Two years of sequencing data outcomes on MROs were available from December 2017 to December 2019. MROs were sequenced at a central facility from 27 hospitals across Queensland. 90% of the 1,783 isolates that were sequenced during the period were from three of the largest Queensland hospitals: RBWH, Queensland Childrens’ Hospital and the Princess Alexandra Hospital. Genetic relatedness was determined by examining the number of core genome single nucleotide polymorphisms (SNP) that differ between any two isolates (pair-wise core genome SNP distance). Genetically related isolates were subdivided into clusters when the SNP distances between them was under a predefined threshold, adjusted for genome size (5 SNPs/mb)^{14 15}. Clustering was evident in all six pathogens and isolates within these clusters demonstrate a high probability that pathogen transmission occurred between patients in the hospital.

Table 1: Parameters values used in estimating the number of hospitalised patients affected by MROs

Variable	Estimate (95%CI)	Source
No. Queensland hospital admissions per quarter	409,972 (348,476, 462,243)	Queensland Health ⁹
Prevalence of all hospitalisations with a HAI	9.9% (8.8%, 11.0%)	Russo (2019) ¹⁰
% of species of all HAIs ^a		
<i>Staphylococcus aureus</i>	13.8% (10.2%, 17.3%)	Russo (2019) ¹⁰
<i>Escherichia coli</i>	8.8% (5.9%, 11.7%)	
<i>Enterococcus faecium</i>	5.8% (3.4%, 8.2%)	
<i>Klebsiella pneumoniae</i>	4.4% (2.3%, 6.5%)	
<i>Enterobacter cloacae</i>	1.9% (0.5%, 3.3%)	
<i>Acinetobacter baumannii</i>	1.1% (0.0%, 2.2%)	
% multidrug resistant ^b		
MRSA	14.4% (13.3%, 17.2%)	Wozniak (2019) ¹¹
ESBL <i>E. coli</i>	5.3% (4.5%, 6.5%)	
VRE	37.8% (26.7%, 49.2%)	
ESBL <i>K. pneumoniae</i>	4.1% (3.6%, 7.7%)	Coombs (2018) ¹²
CPE	4.1% (3.9%, 4.3%)	
CR-Ab	3.2% (2.7%, 3.7%)	
Annual change of species incidence (% points)		
MRSA	0.3	ACSQHC ¹³
ESBL <i>E. coli</i>	0.9	
VRE	-2.8	
ESBL <i>K. pneumoniae</i>	1.0	
CPE	0.0	Coombs (2018) ¹²
CR-Ab	0.0	
Infection fraction ^c		
MRSA	20.6% (18.6%, 22.5%)	Hospital / Clinical Data
ESBL <i>E. coli</i>	30.0% (23.9%, 36.1%)	
VRE	4.6% (2.9%, 6.3%)	
ESBL <i>K. pneumoniae</i>	27.6% (21.1%, 34.0%)	
CPE	35.9% (20.8%, 51.0%)	
CR-Ab	15.2% (4.8%, 25.6%)	
Cluster frequency ^d		
MRSA, ESBL <i>E. coli</i> , ESBL <i>K. pneumoniae</i>	0.02	Sequencing data records
VRE	0.05	
CPE, CR-Ab	0.06	
Decreased cluster size (95%CI)		
MRSA ^d	5.38 (1.37, 9.38)	Sequencing data records This is the estimated drop in cluster size with WGS use
ESBL <i>E. coli</i> ^d	10.25 (2.94, 17.56)	
VRE	8.29 (3.89, 12.68)	
ESBL <i>K. pneumoniae</i>	3.25 (1.23, 5.27)	
CPE	6.33 (-1.20 ^f , 13.87)	
CR-Ab	4.00 (-1.88 ^f , 9.88)	

Note: HAI – Hospital acquired infection, CI – confidence interval, MRO – Multidrug resistant organism, MRSA – Methicillin-resistant - staphylococcus aureus, ESBL - Extended spectrum beta-lactamases, VRE - Vancomycin-resistant Enterococci, CPE - Carbapenemase-Producing Enterobacteriales, CR - carbapenem-resistant, Ab - Acinetobacter baumannii,

^a The HAI percentage of each organism, denominator is total HAIs.

^b Denominator is the total number of the organism detected.

^c The fraction of infections to infections plus colonizations

^d The probability of a cluster detected from all isolates sequenced for that species.

^e Infection control response required cluster size of 3 isolates before action is taken.

^f The negative number does not denote an increase in isolates. Two isolates are required to identify the cluster, so this negative value means that no clusters are identified.

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Identifying SNP differences, through WGS, to investigate MRO outbreaks has become instrumental in revealing the routes of transmission and guiding the infection control response strategy^{16 17}. The number of isolates in a cluster required to begin a response differs with each MRO. Based on current clinical practice, a cluster was acted on when two related isolates of an MRO were identified, except for MRSA and ESBL *E. coli* where three related isolates were required. The number of clusters ranged from 2 to 18 across the pathogens with an average number of patients in each cluster ranging from 5 to 13 (Table 1).

Effectiveness of WGS surveillance

The effectiveness of WGS was estimated when clusters were identified and the information was provided to the infection control team, an outbreak was confirmed, and appropriate infection control measures mobilised. The effectiveness of WGS was a factor of the number of isolates that comprise a cluster, the number of clusters identified, and the expected success of intervening to break the chain of transmission. An implicit assumption in this analysis is that the chain of transmission is broken when the WGS data is acted on immediately. Pathogen transmission is prevented with effective environmental cleaning, patient isolations and contact tracing, which we assume occurs in all cases

The number of patients that could have prevented being infected or colonized was calculated after WGS identified a cluster (2 or 3 patients) and began control measures. The turnaround time for WGS testing was 7 days; this is the time required for WGS to be processed and results made available to the physicians. For example, if the cluster was identified after 2 patients were detected, and the cluster size was 5 then 3 patients could potentially avoid infection providing 7 days had elapsed between patient 2 and 3 in the cluster (Table 1, Supplementary Figure).

Expected deaths

Data on the frequency of deaths in hospital from patients infected with any of the six MROs were obtained from the Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report¹² and ranged from 6.7% for CPE *E. cloacae* to 36.6% for VRE *E. faecium*. Sensitivity analyses were performed on the 95% confidence limits of these mortality rates.

Resource use and costs

Patients who were colonised with an MRO accrued hospital costs for health professional personal protective equipment (PPE), microbiology tests, cleaning and extra infection control nursing time associated with contact precautions. Patients who were infected and showed symptoms accrued

these same costs plus costs for antibiotic treatments and bed closures. PPE was valued at \$50 per day for each patient isolated¹⁸. The colonisation and infection mean length of stay for each MRO ranged from 9 to 43 days (Table 2)¹⁹⁻²⁴. Published estimates for extra length of stay due to infection were used to calculate the additional hospitalisation costs for each MRO (Table 2)^{20 21 23}. These were valued at \$246 per day²⁵. Antibiotic treatments were estimated from clinical advice (for infected symptomatic patients only), and their costs sourced from hospital pharmacy records, the Pharmaceutical Benefit Scheme and published studies^{11 26 27}. Where necessary, costs were inflated to 2019 prices using the Hospital Pricing Index. Sensitivity analyses were performed on the 95% confidence limits of the values and for treatment costs, $\pm 15\%$.

Table 2: Variables used in estimating the cost of MRO screening and treatments

Variable	Estimate (95%CI)	Comment/ Source
Cost of screening for pathogens		
Usual screening - Microbiology test and PCR	\$82 (\$58, \$107)	Elliott (2020) ⁵
WGS - Microbiology test, PCR and WGS	\$437 (\$309, \$565)	Elliott (2020) ⁵
Cleaning and extra nurse time per detection ^a	\$122 (\$90, \$155)	Elliott (2020) ⁵
PPE per day in isolation	\$50 (\$35, \$65)	Otter (2016) ¹⁸
Closed-bed day	\$246 (\$151, \$342)	Page (2017) ^{25*}
Cost of antibiotic treatment per infected patient		
MRSA (Vancomycin) ^b	\$580 (\$409, \$750)	SA guideline ²⁶ / Hospital Pharm
ESBL <i>E Coli</i> . (Meropenem) ^c	\$321 (\$227, \$416)	Wozniak (2018) ²⁸ and Hospital
VRE (Linezolid & Daptomycin) ^d	\$3,433, (\$2,424, \$4,443)	Pharmacy pricing
CPE (Colistin + Meropenem ^e & Gentamicin/Amikacin ^f)	\$2,920, (\$2,061, \$3,778)	Pharmacy infection network ²⁷ and Hospital Pharmacy pricing
CR-Ab (Colistin + tigecycline ^g & Colistin + Meropenem ^e)	\$3,199 (\$2,258, \$4,139)	Viehman (2014) ²⁹ and Hospital Pharmacy pricing
MRSA		
Colonization LOS	29.2 (16.4, 51.9)	Kirwin (2019) ²⁰
Infection LOS	42.7 (23.6, 77.2)	Kirwin (2019) ²⁰
ESBL <i>E coli</i>		
Colonization LOS	16.0 (8.0, 31.0)	Suzuki (2020) ²³
Infection LOS	33.0 (18.0, 64.0)	Suzuki (2020) ²³
VRE		
Colonisation LOS	15.0 (9.0, 30.0)	Tan (2018) ³⁰
Infection LOS	34.0 (29.6, 38.4)	Lloyd-smith (2013) ²¹
ESBL <i>K. pneumoniae</i>		
Colonisation LOS	16.0 (8.0, 31.0)	Suzuki (2020) ²³
Infection LOS	33.0 (18.0, 64.0)	Suzuki (2020) ²³
CPE		
Colonisation LOS	12.0 (3.0, 21.0)	Rodriguez-Acevedo (2020) ^{22*}
Infection LOS	29.0 (22.7, 35.3)	Zhen (2019) ²⁴
CR-Ab		
Colonisation LOS	9.0 (6.0, 22.0)	A'lvarez-Mari'n 2016 ¹⁹
Infection LOS	21.5 (11.5, 42.8)	A'lvarez-Mari'n 2016 ¹⁹
Closed bed days^h		
MRSA	35.2 (16.3, 69.4)	Kirwin (2019) ²⁰

Variable	Estimate (95%CI)	Comment/ Source
ESBL E coli	16.6 (3.6, 30.4)	Suzuki (2020) ²³
VRE	13.8 (10.0, 16.9)	Lloyd-smith (2013) ²¹
ESBL K pneumoniae	16.6 (3.6, 30.4)	Suzuki (2020) ²³
CPE	14.5 (11.4, 17.6)	Assumption ⁱ
CR-Ab	10.8 (5.8, 21.4)	Assumption ⁱ

Note: CI – confidence interval, WGS – whole genome sequencing, LOS – length of stay, PPE – personal protective equipment, MRSA – Methicillin-resistant staphylococcus aureus, ESBL - Extended spectrum beta-lactamases, VRE - Vancomycin-resistant Enterococci, CPE - Carbapenemase-Producing Enterobacterales , CR-Ab - Carbapenem-resistant Acinetobacter baumannii,

*Australian study/data

^a Cleaning is for decontamination of the room and Nursing time is for isolating patient, contact precautions, etc

^b Flucloxacillin administered at 2g IV 6 hourly initially and Vancomycin at 2g

^c Meropenem administered at 1.0-2g for 3 times daily

^d Linezolid administered at 2x0.6 g for 14 days and Daptomycin 0.6g daily

^e Colistin administered at 275mg for 14 days and Meropenem administered at 1.0-2g for 3 times daily

^f Gentamicin administered at 5-7mg/kg for 14 days and Amikacin administered at 15mg/kg

^g Colistin administered at 275mg for 14 days and tigecycline administered at 100mg followed by 50mg every 12 hours

^h Closed bed days was estimated by the excess LOS for infections by each specie.

ⁱ Extra LOS was assumed to be 50% of the infection LOS

Analyses

Analyses comprised of aggregated totals of costs for current practice compared with a strategy of WGS surveillance for the six MROs. Analyses were performed in Excel™. Multiway sensitivity analyses were undertaken for each variable (e.g., organism frequency, MRO rate, cluster frequency, infection fraction etc) and high and low values for the six organisms were used simultaneously for each variable. These values were varied within the 95% confidence limits and results were shown for the overall cost difference between current practice (no WGS) and WGS-surveillance (Table 1). A sensitivity analysis was performed on a quicker 4-day turnaround time for WGS testing. Outcomes were reported for the number of expected patients with colonisations and infections, the associated hospitalisation costs and expected deaths.

Patient and Public Involvement

The research study did not involve patient and public involvement.

Results

An estimated 8,003 patients in Queensland hospitals will be infected with one of six common MROs and 89,535 will be colonised, a total of 97,539 patients in the first year. MRSA and VRE made up the majority of the six MROs (Table 3). The expected number of deaths were 2,032 in Year 1. Over five years, the number of patients infected with these MROs decreased by 15% and the number of

colonisations decreased by 27% overall, primarily due to decreasing drug resistance for VRE (Table 3).

Table 3: Estimated number of Queensland patients with multidrug resistant organisms and deaths from sepsis

	2020	2021	2022	2023	2024
No. annual hospitalisations	1,639,888	1,639,888	1,639,888	1,639,888	1,639,888
No. HAIs	162,349	162,349	162,349	162,349	162,349
No. HAIs from MROs of interest	58,141	58,141	58,141	58,141	58,141
No. patients infected with drug resistant MROs ¹					
MRSA	3,223	3,290	3,357	3,424	3,491
ESBL <i>E. coli</i>	752	881	1,009	1,138	1,267
VRE	3,551	3,288	3,025	2,762	2,499
ESBL <i>K. pneumoniae</i>	292	364	435	507	578
CPE	128	128	128	128	128
CR-Ab	57	57	57	57	57
Total drug resistant MROs of concern	8,003	8,008	8,012	8,017	8,021
Total no. pts colonised with drug resistant MROs	89,536	84,801	80,067	75,332	70,598
Total no. pts expected with infections/colonisations	97,539	92,809	88,079	83,349	78,619
Deaths from sepsis	2032	1982	1932	1881	1831

Note: HAI – Healthcare-associated infection, MRO – Multidrug resistant organism, MRSA – Methicillin-resistant -Staphylococcus aureus, ESBL - Extended spectrum β -lactamases,

VRE - Vancomycin-resistant Enterococci, CPE - Carbapenemase-producing Enterobacterales, CR - carbapenem-resistant, Ab - Acinetobacter baumannii,

1. Adjusted for change in drug resistance rate.

This compares with a strategy of routine WGS surveillance, with a turnaround time of seven days, where WGS use could avoid 2,085 infected patients and 34,641 colonised patients (Table 4). In total, WGS would avoid 36,726 patients infected/colonised in Year 1 decreasing to 26,984 avoided patient infections/colonisations by Year 5. The number of patient deaths avoided were estimated at 650 in Year 1 to 502 by Year 5.

Total costs for the current management of these colonised and infected patients were an estimated \$170.8 million in Year 1, comprising \$8.0 million for conventional microbiology screening, \$11.9 million for cleaning and nursing time, \$44.8 million for closed-bed days, \$91.1 million for the cost of PPE and \$15.0 million for antibiotic treatments (Table 4).

Table 4: Estimated differences in costs AU\$ and patient deaths of current practice versus WGS surveillance

	2020	2021	2022	2023	2024
CURRENT PRACTICE					
Total no. pts expected to have MRO infections/colonis	97,539	92,809	88,079	83,349	78,619
Cost of microbiology screening	\$8,028,283	\$7,638,967	\$ 7,249,651	\$ 6,860,335	\$6,471,019
Cost of cleaning and nursing time	\$11,911,230	\$11,333,618	\$10,756,006	\$10,178,394	\$ 9,600,782
Cost of extra length of stay	\$44,793,430	\$45,297,162	\$45,800,893	\$46,304,625	\$46,808,356
Cost of PPE	\$91,162,386	\$87,836,074	\$84,509,762	\$ 81,183,450	\$77,857,139
Cost of antibiotic treatment of patients	\$14,952,034	\$14,152,425	\$13,352,816	\$12,553,207	\$11,753,598
Total Cost - CURRENT PRACTICE	\$170,847,364	\$166,258,246	\$161,669,129	\$157,080,012	\$152,490,895
Expected no. patient deaths	2032	1982	1932	1881	1831
WGS SURVEILLANCE					
Total no. potentially avoided infections with WGS (pts)	2085	2003	1921	1839	1757
Total no. potentially avoided colonisations with WGS (pts)	34641	32287	29934	27580	25227
Total no. potentially avoided infected/colonised with WGS	36726	34290	31855	29419	26984
Cost of WGS	\$26,575,746	\$25,573,072	\$ 24,570,397	\$23,567,723	\$22,565,049
Cost of cleaning and nursing time	\$7,426,340	\$7,146,152	\$6,865,964	\$ 6,585,777	\$6,305,589
Cost of extra length of stay	\$36,149,780	\$36,881,764	\$37,613,748	\$38,345,732	\$39,077,716
Cost of PPE	\$60,703,607	\$59,267,592	\$57,831,577	\$56,395,563	\$54,959,548
Cost of treating infected patients	\$9,123,437	\$ 8,713,828	\$8,304,219	\$7,894,610	\$7,485,001
Total Cost - WGS Surveillance	\$139,978,910	\$137,582,408	\$135,185,906	\$132,789,404	\$130,392,902
Expected no. patient deaths	1382	1369	1356	1342	1329
Cost savings with WGS Surveillance	\$30,868,454	\$ 28,675,839	\$26,483,223	\$24,290,608	\$22,097,992
Patient deaths avoided	650	613	576	539	502
Costs saved per avoided infection	-\$14,805	-\$14,317	-\$13,787	-\$13,210	-\$12,579
Costs saved per avoided colonisation	-\$891	-\$888	-\$ 885	-\$881	-\$ 876

Compared with a strategy of routine WGS surveillance, sequencing and microbiology costs would be \$26.8 million (\$18.5 million more than standard care), but is offset in the same year by fewer costs for cleaning and nursing, length of stay, PPE and antibiotic treatments (Table 4). The total cost savings were \$30.9 million in Year 1 dropping to \$22.1 million by Year 5. The costs saved for each avoided patient infection was \$6,917 and for each colonization \$475 in Year 1.

The sensitivity analyses showed that when plausible alternative values were used in the analyses, hospital cost savings were always retained, with one exception (Figure 1). The findings were most sensitive to the variation in estimates of preventable patient infections if WGS is undertaken and if this was the lowest value across all six MROs (simultaneously), it would cost an additional \$5.0 million for the WGS strategy. The length of stay for colonisations and organism frequency also changed the base findings by \pm \$10.0 million, but overall cost savings remained. When higher and lower values were used for expected rates of deaths from the six MROs (simultaneously), the deaths potentially avoided ranged from 411 to 893 in Year 1 to 316 to 694 in Year 5.

Discussion

To the best of our knowledge on the incidence of HAIs, MROs and drug resistance rates, nearly 100,000 patients will be infected or colonized with potentially serious bacterial infections in Queensland hospitals each year. This will cost the government \$171 million per year to manage. By routinely using WGS to assist infection control teams to manage patients early in bacterial transmission, the expected cost savings are \$30.9 million per year. Not only will hospital costs be saved but thousands of patients will avoid the suffering from infections and the associated risk of death.

Based on the information from WGS, we identified clusters to observe detection patterns of the six MROs among hospital patients. This differs from observing actual transmission among patients because WGS screening was not undertaken on every patient. Retrospectively, we found WGS was performed on between 13-93% of the MROs, with 13% for each of *S. aureus* and *E. coli*, the most common pathogens. The cost savings are heavily influenced by the cluster sizes and potential to avoid infections/colonisations, breaking the chain of transmission. A quicker testing turnaround is desirable for infection control processes. When we tested the turnaround time from seven days to four days, we saw only two of the six MROs with notable reductions in patients infected, meaning

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detections in most patients screened, were greater than a few days between the first two or three patients.

These findings align with other economic studies looking at the benefits of a WGS surveillance-based infection control program. Kumar *et al.* (2020) findings from a single-institute US study, found WGS surveillance to be less costly and more effective than standard of care. Their results were most sensitive to WGS cost and number of isolates sequenced each year⁶. In the UK, Dymond *et al.* (2019) undertook an economic analysis that modelled MRSA genomic surveillance, compared with current practice, and found cost savings for genomic surveillance of ~£730,000 annually to the NHS⁴. And in Australia, our previous work on an ESBL *E. coli* outbreak in a single hospital also predicted significant cost savings and patient outcomes if WGS was implemented early as standard of care and avoided delays in response⁵. The major criticisms of the previous work in this area are the focus on single organisms or single institutions which can limit the generalisability of the findings and studies are retrospective. Our cost analysis somewhat overcomes these issues by analysing data from Queensland hospitals for state-wide application, including six common MROs in our setting, and we estimated future trends based on expected changes in multidrug resistance rates.

The cluster information from WGS was not available in real-time but part of a demonstration project of prospective WGS in response to suspected outbreaks, to detect clusters before they became established as larger outbreaks. The cluster analysis here was performed retrospectively within a research context. Our cost analysis shows the potential for proactive WGS surveillance to support infection control teams under the premise that testing infrastructure, staffing and fast turnaround times are in place on a wider scale. With the extensive COVID-19 pandemic preparations for widespread testing and additional sequencers now in place for Queensland, this would appear possible for more routine whole-genome pathogen sequencing. An additional benefit of the genomic information are the contributions towards phylogenetic libraries and reporting to share knowledge and information with other jurisdictions and the scientific community.

This study should be viewed with some caution as it depends on the accuracy of the estimates used. For example, it is feasible that the estimates of deaths avoided with WGS may be conflated by the MRO not being the main cause of death if the patient’s underlying clinical condition is severe and advanced. Other than the best available evidence for the estimates used in the analysis, the appropriate way to address this is through sensitivity analyses. To deal with the possible uncertainty in the estimates, 95% confidence limits were tested in sensitivity analyses. These found the cost

savings were stable despite variation in all but one scenario (i.e. low cluster sizes). Estimating the mean length of stay for infections or colonisations is difficult to measure and varies significantly depending on MRO type. Colonization length of stay directly influences infection control nursing time and PPE costs and is shown to be a major driver of these findings, with high patient numbers. Further research is necessary to avoid measurement bias of length of stay estimates for HAIs²². A further issue is the assumption that WGS equipment and infrastructure were available at the outset as these costs are not included in an operational budget impact, but rather, a capital investment. Economies of scale with wider testing and lower testing is seen in the sensitivity analyses covering a lower unit cost for WGS, however further streamlining of workflows could see testing in future as low as AU\$150 per isolate. Overall, we suggest the findings are conservative because WGS testing was only used infrequently as a total percentage of MRO isolates and if screening were higher, more infections and therefore higher cluster sizes would be apparent (at reasonable cost). The expected consequences of a WGS strategy is also likely to be conservative and other MROs were excluded in the analysis. Furthermore, it is possible that an organism can contribute to more than one type of HAI and therefore, that the impacts of prevention may also be greater.

Implementation of WGS into routine infection control practice would require standardised algorithms leading to early alarms and detection of problems, and intervention for all hospitals. Although many hospitals do have systems and decision rules currently in place, a key issue is whether infection control teams would immediately and effectively respond on receiving these advanced data. This is uncertain, as is any significant organisational change, and would require infection control teams to undergo training and time to transition to new protocols. Our analysis assumes full adherence to a new scenario as presented here, as if it were established, and it is recognised this is the result of effective change and uptake by hospitals. Nevertheless, predictions about resource use and costs that might result from routine WGS are useful for decision-makers to understand whether it is warranted on an economic basis to proceed further with new resource allocations.

Conclusion

The proactive use of WGS surveillance for infection control of common MROs was estimated to be cost saving for hospitals and beneficial for patients. This study has implications for government resource allocation decisions and establishes a favourable value proposition for adopting pathogen WGS into routine clinical practice in Queensland.

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Author contributions

LG & TE conceived the study aim and purpose. TE undertook the main analyses with assistance from LG. BF, PR, DP, BM provided data for this study, critically reviewed the study, contributed to drafting the paper and provided subject matter expertise. PH, DP & BF provided clinical and scientific expertise. All authors contributed to drafting the manuscript and reviewed the final version.

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Competing Interests Statement

The authors have no conflicts of interest to declare.

Data sharing statement

The Excel worksheet and analysis file are available upon request to the authors.

Figure Legends

Figure 1: Tornado diagram of change in the main analysis cost savings AU\$30.9 million, with higher and lower input values

Note: HAIs – hospital-associated infections, WGS – whole-genome sequencing, PPE – personal protective equipment.

Supplementary Figure: Illustration of clusters and avoidable infections

References

1. Mitchell BG, Shaban RZ, MacBeth D, et al. The burden of healthcare-associated infection in Australian hospitals: A systematic review of the literature. *Infect Dis Health* 2017;22(3):117-28. doi: 10.1016/j.idh.2017.07.001. Epub 17 Aug 15.
2. Australian Institute of Health and Welfare (AIHW). General Record of Incidence of Mortality (GRIM) data, Cat. no: PHE 229, Canberra: AIHW; 2019 [Available from: <https://www.aihw.gov.au/reports/life-expectancy-deaths/grim-books> accessed 3/6/2020 2020.
3. Li LM, Grassly NC, Fraser C. Genomic analysis of emerging pathogens: methods, application and future trends. *Genome biology* 2014;15(11):541. doi: 10.1186/s13059-014-0541-9 [published Online First: 2014/11/25]
4. Dymond A, Davies H, Mealing S, et al. Genomic surveillance of methicillin-resistant *Staphylococcus aureus*: a mathematical early modelling study of cost effectiveness. *Clinical Infectious Diseases* 2019:ciz480. doi: 10.1093/cid/ciz480
5. Elliott TM, Lee XJ, Foeglein A, et al. A hybrid simulation model approach to examine bacterial genome sequencing during a hospital outbreak. *BMC Infect Dis* 2020;20(1):72. doi: 10.1186/s12879-019-4743-3.
6. Kumar P, Sundermann AJ, Martin EM, et al. Method for economic evaluation of bacterial whole genome sequencing surveillance compared to standard of care in detecting hospital outbreaks. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2020 doi: 10.1093/cid/ciaa512 [published Online First: 2020/05/06]
7. Gordon LG, White NM, Elliott TM, et al. Estimating the cost of genomic sequencing in cancer control. *BMC Health Services Research* 2020;DOI: 10.1186/s12913-020-05318-y
8. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value in Health* 2014;17(1):5-14. doi: <https://doi.org/10.1016/j.jval.2013.08.2291>
9. Health Q. Quarterly hospital activity information for October, November, December 2019: Queensland government; [cited 2020 24/04/2020]. Available from: <http://www.performance.health.qld.gov.au/Hospital/HospitalActivity/99999>.
10. Russo PL, Stewardson AJ, Cheng AC, et al. The prevalence of healthcare associated infections among adult inpatients at nineteen large Australian acute-care public hospitals: A point prevalence survey. *Antimicrobial Resistance and Infection Control* 2019;8(1) doi: 10.1186/s13756-019-0570-y
11. Wozniak TM, Bailey EJ, Graves N. Health and economic burden of antimicrobial-resistant infections in Australian hospitals: A population-based model. *Infection Control and Hospital Epidemiology* 2019;40(3):320-27. doi: 10.1017/ice.2019.2
12. Coombs G BJ, Daley D, Collignon P, Cooley L, Gottlieb T, Iredell J, Kotsanas D, Nimmo G and Robson J on behalf of the Australian Group on Antimicrobial Resistance and Australian Commission on Safety and Quality in Health Care. Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report. Sydney: Australian Commission on Safety and Quality in Health Care, 2019.
13. Care ACoSaQIH. Australian Passive Antimicrobial Resistance Surveillance. First report: multi-resistant organisms. Sydney:: ACSQHC, 2018.
14. Octavia S, Wang Q, Tanaka MM, et al. Delineating community outbreaks of *Salmonella enterica* serovar Typhimurium by use of whole-genome sequencing: insights into genomic variability within an outbreak. *J Clin Microbiol* 2015;53(4):1063-71. doi: 10.128/JCM.03235-14. Epub 2015 Jan 21.
15. Stinear TP, Holt KE, Chua K, et al. Adaptive change inferred from genomic population analysis of the ST93 epidemic clone of community-associated methicillin-resistant *Staphylococcus aureus*. *Genome Biol Evol* 2014;6(2):366-78. doi: 10.1093/gbe/evu022.

16. Chapman P, Forde BM, Roberts LW, et al. Genomic Investigation Reveals Contaminated Detergent as the Source of an Extended-Spectrum- β -Lactamase-Producing *Klebsiella michiganensis* Outbreak in a Neonatal Unit. *Journal of clinical microbiology* 2020;58(5) doi: 10.1128/jcm.01980-19 [published Online First: 2020/02/28]
17. Roberts LW, Harris PNA, Forde BM, et al. Integrating multiple genomic technologies to investigate an outbreak of carbapenemase-producing *Enterobacter hormaechei*. *Nature communications* 2020;11(1):466. doi: 10.1038/s41467-019-14139-5 [published Online First: 2020/01/26]
18. Otter JA, Burgess P, Davies F, et al. Counting the cost of an outbreak of carbapenemase-producing Enterobacteriaceae: an economic evaluation from a hospital perspective. *Clinical Microbiology and Infection* 2017;23(3):188-96. doi: <https://doi.org/10.1016/j.cmi.2016.10.005>
19. Álvarez-Marín R, López-Rojas R, Márquez JA, et al. Colistin dosage without loading dose is efficacious when treating carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia caused by strains with high susceptibility to colistin. *PLoS ONE* 2016;11(12) doi: 10.1371/journal.pone.0168468
20. Kirwin E, Varughese M, Waldner D, et al. Comparing methods to estimate incremental inpatient costs and length of stay due to methicillin-resistant *Staphylococcus aureus* in Alberta, Canada. *BMC Health Services Research* 2019;19(1) doi: 10.1186/s12913-019-4578-z
21. Lloyd-Smith P, Younger J, Lloyd-Smith E, et al. Economic analysis of vancomycin-resistant enterococci at a Canadian hospital: assessing attributable cost and length of stay. *The Journal of hospital infection* 2013;85(1):54-9. doi: 10.1016/j.jhin.2013.06.016 [published Online First: 2013/08/08]
22. Rodriguez-Acevedo AJ, Lee XJ, Elliot TM, et al. Hospitalization costs for patients colonized with carbapenemase-producing Enterobacterales during an Australian outbreak. *Journal of Hospital Infection* 2020 doi: <https://doi.org/10.1016/j.jhin.2020.03.009>
23. Suzuki H, Perencevich EN, Nair R, et al. Excess length of acute inpatient stay attributable to acquisition of hospital-onset Gram-negative bloodstream infection with and without antibiotic resistance: a multistate model analysis. *Antibiotics* 2020;9(2) doi: 10.3390/antibiotics9020096
24. Zhen X, Lundborg CS, Sun X, et al. The Clinical and Economic Impact of Antibiotic Resistance in China: A Systematic Review and Meta-Analysis. *Antibiotics (Basel)* 2019;8(3):115. doi: 10.3390/antibiotics8030115
25. Page K, Barnett AG, Graves N. What is a hospital bed day worth? A contingent valuation study of hospital Chief Executive Officers. *BMC health services research* 2017;17(1):137-37. doi: 10.1186/s12913-017-2079-5
26. Health SA. *Staphylococcus aureus Bacteraemia (SAB) Management Clinical Guideline*. Government of South Australia, 2019.
27. Network PI. GUIDANCE ON TREATMENT OF CARBAPENAMASE PRODUCING ENTEROBACTERIACEAE UK Clinical Pharmacy Association 2016 [Available from: <https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/UKCPA%20CPE%20Guidance.pdf> accessed 16/04/2020.
28. Wozniak TM. Clinical management of drug-resistant bacteria in Australian hospitals: An online survey of doctors' opinions. *Infection, Disease & Health* 2018;23(1):41-48. doi: <https://doi.org/10.1016/j.idh.2017.11.003>
29. Viehman JA, Nguyen MH, Doi Y. Treatment options for carbapenem-resistant and extensively drug-resistant *Acinetobacter baumannii* infections. *Drugs* 2014;74(12):1315-33. doi: 10.1007/s40265-014-0267-8
30. Tan D, Htun HL, Koh J, et al. Comparative Epidemiology of Vancomycin-Resistant Enterococci Colonization in an Acute-Care Hospital and Its Affiliated Intermediate- and Long-Term Care

Facilities in Singapore. *Antimicrobial Agents and Chemotherapy* 2018;62(12):e01507-18. doi:
10.1128/AAC.01507-18

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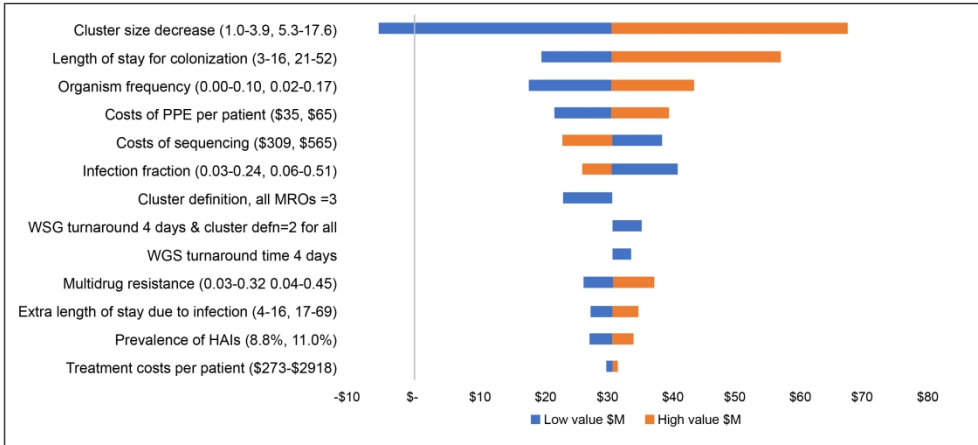
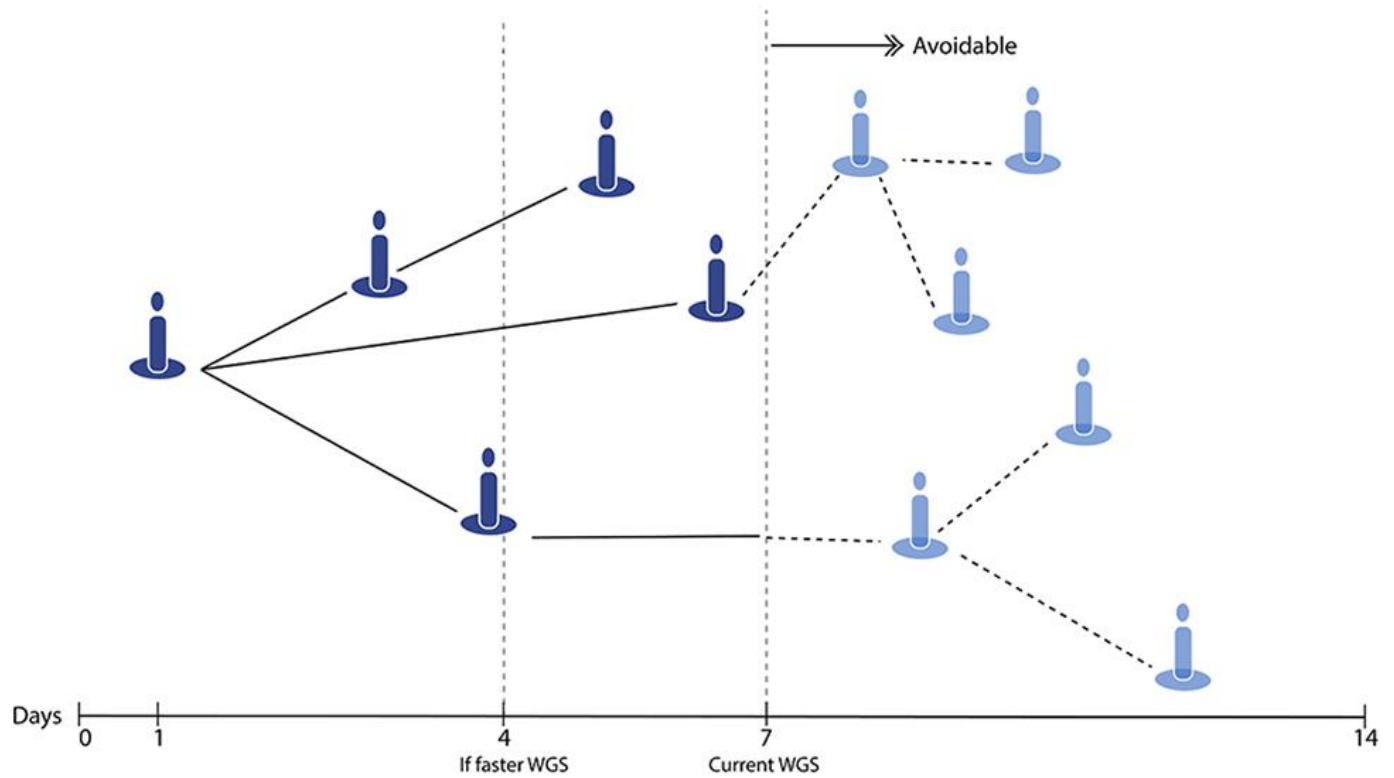


Figure 1: Tornado diagram of change in the main analysis cost savings AU\$30.9 million, with higher and lower input values

269x126mm (300 x 300 DPI)



CHEERS Statement Checklist

Manuscript 'Budget impact analysis of routinely using whole-genomic sequencing of six multidrug-resistant bacterial pathogens in Queensland, Australia'

Section/item	Item no.	Recommendation	Reported on page no./line no.
Title and abstract			
Title	1	Identify the study as an economic evaluation, or use more specific terms such as "cost-effectiveness analysis" and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions	2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4-5
Methods			
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analyzed including why they were chosen.	5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	n/a
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	n/a
	11b	Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	5-10
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	n/a
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	n/a
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	5-10
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	8-9
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	n/a

Section/item	Item no.	Recommendation	Reported on page no./line no.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytic model.	n/a
Analytic methods	17	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Tables 1-2 5-10
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Tables 3-4
Characterizing uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective).	n/a
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	13 Figure 1
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	n/a
Discussion			
Study findings, limitations, generalizability and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	13-15
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	16
Conflicts of interest	24	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	16